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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/726,571	12/04/2003	Hasan Khatib	2901803.3	5115
69219 7590 04/09/2007 BAKER DONELSON BEARMAN CALDWELL & BERKOWITZ, PC 555 11TH STREET, NW 6TH FLOOR WASHINGTON, DC 20004			EXAMINER CHO, DAN SUNG C	
			ART UNIT 1634	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/726,571

Applicant(s)

KHATIB, HASAN

Examiner

Dan-Sung C. Cho

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 12 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Currently, claims 1-29 are pending. Claims 1-11, 22-24, 26-27 have been withdrawn as drawn to non-elected subject matter. In addition, claims 13-21, 25, 28, 29 of elected Group II and the linking claims 24 and 27 have been withdrawn as drawn to non-elected combination of SNPs. Claim 12 and polymorphic sequence at position 164 are under consideration. Amendment to Claim 12 in a paper filed on 3/22/2007 is acknowledged.

2. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are reiterated or newly applied as necessitated by the amendment. They constitute the complete set being presently applied to the instant Application.

All rejections are maintained. Response to Applicant's arguments follows. This action is **FINAL**.

Maintained Rejections

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

“Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.”

The nature of the invention and breadth of claims

Claim 12 is drawn to a method of SNP detection for bovine PI position 164. The invention is in a class of invention which the CAFC has characterized as “the unpredictable arts such as chemistry and biology.” *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (*Genetics in Medicine*. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing

conclusions from a single report of an association between a genetic variant and disease susceptibility.

Beauchemin et al. teaches that an evaluation of bovine DNA polymorphisms involving bovine growth hormone does not predict bovine growth and carcass characteristics (Beauchemin et al., 2006, Genetics and Molecular Research, 5:438-447; p 435, lines 2-4). When 430 animals were analyzed for two SNPs and two RFLP polymorphisms, none of the genotype was a significant source of bovine growth and carcass characteristics including an Msp-I RFLP (p 443, line 10). In addition DNA polymorphisms discovered in Bos taurus cattle may not be applicable to Bos indicus cattle (p444, lines 2-3).

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpk15 and cadpk16 are not associated with the disease, however cadpk17 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the

gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that the SNP at position 164 of bovine PI can be used for milk production trait association or any other use. The specification teaches haplotypes and their use in association study for bovine milk production but not any specific use of bovine PI genotype at position 164. The specification teaches PI haplotype with direct phased genotype data for positions 164, 269, 284, 407 and 989 and milk trait association (Tables 3 to 5); however, the direct association of the genotype at position 164 of bovine PI and milk production trait or any other trait or use is not disclosed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. While the position 164 of bovine PI can be detected with direct sequencing as disclosed in the specification, the applicant fails to provide enablement for use of the method of detecting SNPs at position 164 of bovine PI.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses how to genotype bovine PI 164 SNPs but not how to use any SNP method. The specification teaches how to detect SNP at 164 but does not teach the skilled artisan to use the analysis. For example, if the skilled artisan determines a cow has an A at 164, it is unclear how the skilled artisan would use this information.

Working Examples

The specification has no working examples of any bovine PI genotype at position 164 use; the specification only discloses the use for the PI haplotype or 5 genotype combinations. The specification analyses only 164 in combination with 4 other markers to get a haplotype.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied. Whether the method of SNP detection at bovine PI position 164 can be used for any traits or other use will require studying any potential use or traits that may be associated with the SNP. Freedman et al. teaches that previously reported BRACA2 SNPs with positive breast cancer association, the HH genotype of the N372H polymorphism and the M784V polymorphisms, had no positive associations with breast cancer in their study of more than 4,200 cases (p 2438, left column, paragraph 1), possibly because of ethnic background difference. However, Freedman et al. found instead reports positive associations with cosegregating haplotypes in blocks 1-3, the ancestrally related haplotypes 3d, 3f and 3i, and multiple SNPs that resided on this haplotype pattern (p 2438, left column, paragraph 2). Therefore the skilled artisan needs to determine multiple SNPs along with bovine PI SNP164, determine haplotypes and their association with milk production among different cattle populations (Bos taurus vs not Bos indicus).

This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

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Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the SNP and its association with phenotypic traits or other use is not disclosed in the specification. Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Further, the prior art and the specification provides insufficient guidance to overcome the art recognized. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Response to arguments

4. The response asserts on page 7, para 3-4, that the T genotype for SNP position 989 is strongly correlated to significant increase in milk productive life and decrease in somatic cell score in the milk in a paper filed on 3/22/2007. This argument has been thoroughly reviewed but was not found persuasive because the genotype position is not the position under examination. The response states that the applicant understand that

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the instant rejection is based on whether the claimed method can be used by one of ordinary skills in the art without undue experimentation in para 5, lines 2-4. Then the applicant alleges that there is a strong correlation between SNP position at 989 with milk production traits. However it is noted that the elected position is not 989 but 164. Claim 12 is amended to recite "A method for selectively breeding dairy cattle for improved milk production trait". The response further asserts on page 17, para 5, that the amendment to recite the cattle breeding method in the claim and the strong evidence that SNP position 989 correlating with marked increase in milk production trait have overcome the instant rejection. This argument has been thoroughly reviewed but was not found persuasive because the SNP position 989 allegedly associated with the milk production traits is not the elected position. Evidence of any association of other SNP to milk production trait is not relevant to whether similar alleged association exists for the elected position 164 with milk production trait. For these reasons and the reasons already made of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claim 12 is rejected under 35 U.S.C. 102(a) as being anticipated by IBISS (IBISS, The Interactive Bovine In Silico SNP database, CSIRO, Hawken, R, Barris W.

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and Dalrymple B. Pileup alignment dated July, 21, 2003, URL:

<http://livestockgenomics.csiro.au/IBISS3/msff/btcn3197.txt>). IBISS teaches a total of 48,565 bovine SNPs of which 17,344 SNP are represented in more than one sequence and of which 3,372 SNPs have amino acid changes that are represented in more than one sequence. One of the bovine SNP entries identified by IBISS on July 21, 2003 is btcn3197 which is for Bos taurus serine (or cysteine) proteinase inhibitor, clade A (alpha-1antiproteinase, antitrypsin), member 1 (SERPINA1), mRNA or proteinase inhibitor (PI) (URL: <http://livestockgenomics.csiro.au/IBISS3/msff/btcn3197.txt>).

Btcn3197 is the bovine PI sequence with extra nucleotide sequences upstream of position 1 of SEQ ID NO:1 of the instant application.

Response to arguments

6. Claim 12 is amended to recite "A method for selectively breeding dairy cattle for improved milk production trait". The response asserts on page 7, para 6, that because of the amendment to the claim and because the reference on the record does not teach or suggest a cattle breeding method, the rejection has been obviated. This argument has been thoroughly reviewed but was not found persuasive because the amended claim has two active steps wherein, first, the sequence of the position 164 of SEQ ID NO: 1 is determined, and, second, the determined sequence is compared to the nucleotide identity at a corresponding position of SEQ ID NO: 1. Therefore the reference teaches the both recited steps and anticipates the instant amendment. The preamble is not given any weight in the amended claim because the amended claim does not recite any positive steps for selectively breeding dairy cattle for improved milk

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production trait. For these reasons and the reasons already made of record, the rejection is maintained.

New Rejection necessitated by amendment

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Amended Claim 12 is newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 12 is indefinite because it is unclear whether the claim is drawn to a method for selectively breeding dairy cattle for improved milk production trait or a method of determining and comparing sequences. The preamble states that the method is for selectively breeding dairy cattle for improved milk production trait but the final process step is to determine a sequence and to compare to a reference sequence. Therefore the claims are unclear as to whether the method is a method for selectively breeding dairy cattle for improved milk production trait or a method of determining and comparing sequences.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

8. **Claim 12 is not allowed.**

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Dan-Sung C. Cho whose telephone number is (571) 272-9933. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). The Central Fax Number for official correspondence is (571) 273-8300.



Dan-Sung C. Cho
Examiner


JEHANNE SITTON
PRIMARY EXAMINER

3/30/07